Exhibit 7

Preliminary Experience With Paclitaxel (TAXOL®) Plus Recombinant Human Granulocyte Colony-Stimulating Factor in the Treatment of Breast Cancer

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Single-agent paclitaxel (TAXOL®) was administered to 79 patients with stage IV breast cancer. Twenty-eight patients had no prior chemotherapy (for metastatic disease), and 51 patients had extensive exposure to other chemotherapeutic agents before beginning the 24-hour paclitaxel infusion. Routine use of recombinant human granulocyte colony-stimulating factor helped to ameliorate neutropenia, the dose-limiting toxicity, in some cases. Other toxicity was generally mild to moderate. Paclitaxel was more active in patients whose stage IV disease had not yet been exposed to chemotherapy, but activity was seen in the patients previously treated extensively as well. There is a strong clinical suggestion of non–cross-resistance with doxorubicin. In one case, an excellent response in previously irradiated skin was seen. Paclitaxel is a very promising agent for the treatment of metastatic breast cancer.

ONE OF THE MOST interesting new drugs to enter clinical trials against cancer is paclitaxel (TAXOL®), a diterpene derived from the bark of *Taxus brevifolia*. This agent promotes the formation of tubulin dimers and inhibits the depolymerization of microtubules, which kills cancer cells in vitro[1-4] and in xenograft models.[5]

Paclitaxel has been found to have significant activity against human metastatic breast cancer. Holmes et al[6] treated 25 metastatic breast cancer patients with paclitaxel 250 mg/m^2 given via 24-hour continuous intravenous infusion every 3 weeks. These patients had received only one prior chemotherapy regimen, either as adjuvant treatment or for stage IV disease. An objective response rate of 56% (95% confidence interval, 35% to 76%) was observed, with 12% complete responses (CRs) and 44% partial responses (PRs). Disease progression on initial exposure to paclitaxel occurred in only 8% of patients. Dose reductions, mostly to 200 mg/m^2, were needed predominantly for neutropenia (absolute neutrophil count, $<250 \times 10^6$/L). Nonhematologic toxicity was generally mild: grade 1 to 2 sensory peripheral neuropathy occurred in 88% of patients and was reversible. A syndrome of myalgias and arthralgias occurred in the majority of patients, but was tolerable.

Motivated by this report, we began studies of paclitaxel as initial chemotherapy and as salvage chemotherapy for stage IV breast cancer. Because myelosuppression had been the dose-limiting event in the trial by Holmes et al[6] and was notable in the first two patients we treated with paclitaxel, recombinant human granulocyte colony-stimulating factor (rhG-CSF) was used routinely in all subsequent regimens. Our preliminary results confirm that paclitaxel is very active against human breast cancer and should be developed rapidly for use in the management of this disease.

PACLITAXEL AS INITIAL THERAPY

Materials and Methods

In this study, paclitaxel was used as first chemotherapy for patients with histologic evidence of breast cancer and documentation of stage IV disease occurring 12 or more months after cessation of postoperative adjuvant chemotherapy (if any). Patients were excluded if they received more than one prior hormone therapy in the adjuvant setting or as treatment for metastatic disease. Enrollment criteria included measurable, nonirradiated lesion(s); radiotherapy had to have ended 4 weeks previously, with no more than 30% of the marrow-bearing skeleton treated; all central nervous system metastases had to have been treated and no symptomatic lymphangitic lung metastases or carcinomatous meningitis could have been present; and patients had to have adequate renal and liver function, no hypercalcemia, and no other serious medical,

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surgical, or psychiatric condition. Full informed consent was obtained from all patients.

Twenty-eight patients accrued to study between April and October 1991. Table 1 details the characteristics of these patients and those in the salvage paclitaxel trial. The median age was 52 years (range, 30 to 67 years) and the median Karnofsky performance status was 90% (range, 70% to 100%). On entry most patients had extensive disease: the mean number of metastatic sites was two, with 82% of patients having two or more organ system sites of metastases and 39% having three or more. Prior postoperative adjuvant therapy had been used in 58% of patients.

The median interval between the end of adjuvant therapy and the initiation of paclitaxel was 20 months (range, 12 to 47 months). Half of the patients who had prior adjuvant therapies had received doxorubicin. Two patients had received vincristine in the adjuvant setting, one with a doxorubicin regimen and the other with a CMF (cyclophosphamide, methotrexate, 5-fluorouracil) regimen that also included prednisone. Eleven patients had received prior hormone therapy: five as adjuvant treatment, two for stage IV disease, and four in both settings.

We used published phase I data[7,8] to choose a starting dose of paclitaxel of 250 mg/m^2 given as a continuous 24-hour intravenous infusion every 21 days. The drug was supplied by the National Cancer Institute in polyoxyethylated castor oil (Cremophor EL, Sandoz, East Hanover, NJ) and ethanol. We diluted the drug to 0.3 to 1.2 mg/mL in 5% dextrose or 0.9% saline solution. For administration, in-line filters (0.2 μm, IVEX-2; Abbott Laboratories, Abbott Park, IL), glass containers, and polyethylene-lined nitroglycerine tubing were used. Dosage escalations and reductions were planned on the basis of toxicity. For all but the first two patients rhG-CSF (Amgen Inc, Thousand Oaks, CA) was given as 5 μg/kg/d subcutaneously on days 3 through 10.

When we began our study we were aware that the administration of drugs in Cremophor EL has been associated with hypersensitivity reactions. This reaction is probably due to histamine release rather than true allergy because it is often seen on first exposure and may not recur on rechallenge with subsequent courses of treatment.[9] We attempted to prevent this complication by using the well-established regimen of dexamethasone 20 mg orally at hours −14 and −7, and cimetidine 300 mg and diphenhydramine hydrochloride 50 mg intravenously at hour −1, prior to the paclitaxel infusion over hours 0 through 24.[4,10-12] Blood levels were measured to determine whether response and/or toxicity correlated with plasma levels of the parent compound. These pharmacologic data will be reported separately.

The goal of our study was to determine response rate, not response duration. This plan was motivated by a need to conserve drug, which was in short supply when our study was initiated. Accordingly, treatment was planned to be terminated after two cycles beyond best response or 10 cycles if the disease was stable.

Baseline data and response were measured by history, physical examination, complete blood cell count, biochemical tests of renal and liver function, lactate dehydrogenase, uric acid, serum calcium and phosphorus, carcinoembryonic antigen, CA 15-3, electrocardiogram, chest radiograph, and radiologic imaging of index lesions as indicated. Premenopausal women were screened for pregnancy by determination of the level of beta-human chorionic gonadotropin.

Table 1. Characteristics of Patients Receiving Paclitaxel as Initial (Trial 1) or Salvage (Trial 2) Treatment of Stage IV Breast Cancer

	Trial 1 Paclitaxel 250 mg/m^2 + G-CSF	Trial 2 Paclitaxel 200 mg/m^2 + G-CSF
No. of evaluable patients	26	52*
Median age, yr (range)	52 (30-67)	47 (26-73)
Median Karnofsky performance status (range)	90% (70%-100%)	70% (60%-90%)
% Premenopausal patients	32	14
Sites of metastatic disease (%)		
Bone	54	47
Lung	36	45
Liver	39	33
Lymph nodes	57	43
Soft tissue/skin	46	47
Median no. of metastatic sites (range)	2 (1-5)	3 (1-7)
Visceral-dominant disease (%)	62	55
No. of patients with chemotherapy		
Adjuvant	16	27
Doxorubicin based	8	
CMF variants	8	
No adjuvant	10	
Advanced		51†
% Patients with prior radiotherapy	54	67

* Fifty-two patients evaluable for toxicity; 51 evaluable for response.

† Median of three regimens (range, two to six regimens).

Results

Responses. Per protocol requirement, two patients were not evaluable for response: in one case the patient had received two prior hormone therapies for metastatic disease (she had stable disease while receiving paclitaxel) and in the other case an unrelated automobile accident caused pain in the cervical spine. Objective responses by standard criteria were observed in 16 of the 26 evaluable patients (62%; 95% confidence interval, 41% to 80%) (Table 2). There were three (12%) CRs: lymphadenopathy and pleural effusion, lymphadenopathy, and lymphadenopathy and skin in a chest wall that had previously received radiotherapy. The 13 (50%) PRs were seen in visceral, osseous, cutaneous, and nodal sites. Responses in bone were associated with marked relief of pain.

Ten of 16 patients (63%) who had received prior adjuvant chemotherapy responded. This

Table 2. Therapeutic Responses to Paclitaxel as Initial (Trial 1) or Salvage (Trial 2) Treatment of Stage IV Breast Cancer

Response	Trial 1 Paclitaxel 250 mg/m² + G-CSF		Trial 2 Paclitaxel 200 mg/m² + G-CSF	
	No. of Patients	% Patients (95% Confidence Interval)	No. of Patients	% Patients (95% Confidence Interval)
No. evaluable	26		51	
CR	3	12 (2-30%)	0	
PR	13	50 (30-70%)	11	22 (11-35%)
CR + PR	16	52 (41-80%)	11	22 (11-35%)
Minor	4		9	
Stable	0		17	
Disease progression	6		14	

included one CR and four PRs among eight patients who had received prior doxorubicin-containing adjuvant therapy and two CRs and three PRs among eight patients who had received CMF variants.

The median time to first objective response was 5 weeks (range, 1 to 14 weeks) and the median time to best response was 6 weeks, although some patients responded quite late (range, 1 to 14 weeks). Hormone receptor status or prior hormone therapy did not influence the probability of response. The median age of responders was younger (45.5 years; range, 30 to 67 years) than that of nonresponders (55 years; range, 37 to 64 years).

Adverse events. More than half of the patients experienced a neutrophil nadir less than 500 $\times 10^6$/L in the first cycle of administration. The first two patients, who did not receive rhG-CSF, experienced neutropenic nadirs less than 200 $\times 10^6$/L at 2 weeks and did not recover for an additional week. We administered rhG-CSF for all subsequent patients in all subsequent cycles. This resulted in a median of just 2 days of such neutropenia, the nadir occurring approximately 1 week after treatment. With rhG-CSF, one patient's granulocyte nadir was sufficiently high that the paclitaxel dose was escalated to 300 mg/m^2. In cycle 2, just under half of the patients had their doses reduced. Twenty-seven patients received more than one course. Approximately one third of these patients were able to receive subsequent therapy without dose reduction. The median dose of paclitaxel in the third and subsequent cycles was 200 mg/m^2. In this trial, only one patient developed significant thrombocytopenia (Table 3). Because hematologic toxicity was so rapidly reversible, treatment was never delayed because of slow recovery.

Other adverse effects of paclitaxel included generalized alopecia in all patients and, in most patients, mild myalgias, arthralgias, and peripheral neuropathy (<grade 2). Table 3 shows nonhematologic toxicities of grade 3 or worse. Only one patient developed grade 3 nausea. She was found to have an expanding pericardial effusion, which may have contributed to the nausea, since when the effusion was treated surgically the nausea abated and did not return in subsequent cycles. In our small experience (two patients), prior exposure to vincristine did not predispose patients to paclitaxel neuropathy.

Eight of 178 (4.5%) treatment cycles resulted in hospital admission for neutropenic fever. Twenty-two patients (79%) never required hospitalization for neutropenic fever. One patient with extensive hepatic metastases was hospitalized for mucositis, dehydration, pancytopenia, and fever. This patient had a peak paclitaxel level

Table 3. Toxicity in Patients Receiving Paclitaxel as Initial (Trial 1) or Salvage (Trial 2) Treatment of Stage IV Breast Cancer

	Trial 1 Paclitaxel 250 mg/m² + G-CSF	Trial 2 Paclitaxel 200 mg/m² + G-CSF
No. of evaluable patients	28	52
% Cycles with febrile neutropenia	4.5	6.6
% Patients with grade 4 thrombocytopenia	3.6	19.2
% Patients with grade ≥3 nonhematologic toxicities		
Neuropathy	0	5.8
Myalgia/arthralgia	0	7.7
Fatigue	7.1	11.5
Mucositis	3.6	7.7
Nausea/vomiting	3.6	2.9
Hypersensitivity	0	0
Cardiac	0	0

in plasma that was significantly higher than the median for all patients.

Recalling that paclitaxel was discontinued for progressive or stable disease once maximum response was documented, the median number of courses administered per patient was six (range, one to 15 courses). We observed no hypersensitivity reactions, no hemodynamic instability, and no cardiac toxicity.

PACLITAXEL AS SALVAGE THERAPY

Materials and Methods

Having observed the considerable activity of paclitaxel in the previous study, we turned to the study of tumors with extensive prior exposure to chemotherapeutic agents. Our second trial was open only to patients whose disease had proven refractory to at least two prior regimens, one of which had to contain an anthracycline or anthracenedione. Because we expected more severe hematologic toxicity in patients with prior chemotherapy, we chose a starting dose of 200 mg/m^2 given by 24-hour infusion every 21 days, using premedications and posttreatment rhG-CSF as in our previous study.

Fifty-two patients accrued to trial between February and April 1992. Table 1 shows the characteristics of patients in the second trial. The median age was 47 years (range, 26 to 73 years) and the median Karnofsky performance status was 70% (range, 60% to 90%). Patients had received a median of three prior chemotherapy regimens (range, two to six regimens) and 34 patients (67%) had received prior radiation therapy for stage IV disease. Seven patients (14%) had received prior chemotherapy at doses sufficiently myelotoxic that rescue by reinfusion of autologous bone marrow or peripheral blood progenitor cells with hematopoietic growth factors had been used.

Twenty-two patients had breast cancer with demonstrated primary resistance to doxorubicin or mitoxantrone. Twenty-seven had previously responded transiently to doxorubicin or mitoxantrone but then had disease progression, and two had stable disease (one given each agent). The median number of metastatic organ system sites was three (range, one to seven sites). Eighty-six percent of patients had more than one involved site. Sites of metastases included bone in 47% of patients, lymph nodes in 43%, liver in 33%, skin or soft tissue in 47%, and lung or pleura in 45%.

Results

It is still early in the conduct of this study, so estimates of rates of response and toxicity may change considerably with more experience. As of September 1, 1992, 228 cycles of paclitaxel had been delivered. The median number of cycles per patient was four (range, one to 10 cycles).

Responses. Of the 51 patients evaluable for response, 11 achieved PRs (22%; 95% confidence interval, 11% to 35%) in all sites of metastatic disease (Table 2). This is a low estimate since responses continue to evolve in the 23 patients still on study. (Further responses will be updated in a subsequent report.) The median response duration is already in excess of 10 weeks, and many patients continue in response. Responses have been seen as frequently in patients whose disease was sensitive to anthracycline or anthracenedione (5 of 27, 18.5%) as in those whose disease was primarily refractory to these agents (four of 22, 18.1%). Responses have been observed in one patient whose cancer had been stable on doxorubicin and in one patient whose cancer had been stable on mitoxantrone.

Adverse events. Consistent with our experience in the prior study, the dose-limiting toxicity of paclitaxel therapy was myelosuppression, especially an absolute neutrophil count less than 250×10^6/L, but also a platelet count less than 50×10^9/L. Fifteen of 228 cycles (6.6%) in 18% of patients were associated with febrile leukopenia (Table 3). Only one of the 28 patients who had not had prior stage IV chemotherapy developed notable thrombocytopenia during paclitaxel therapy in trial 1. However, 10 patients who had prior stage IV chemotherapy developed thrombocytopenia less than 50×10^9 cells/L after paclitaxel and required dose reductions. Thus far, 24 of 51 patients (47%) have required dose reductions, almost all because of hematologic toxicity. One patient required reduction of dose because of profound weakness, two for stomatitis, and one for severe myalgia and arthralgia.

Largely because of toxicity, no patient has yet had the dose escalated above 200 mg/m^2. Eleven patients have had their doses reduced to 150 mg/m^2, and two have received 125 mg/m^2.

Nonhematologic toxicity (Table 3) has been similar to that observed in the earlier experience, but slightly more severe. Four patients had grade 3 or 4 mucositis and four patients experienced grade 3 myalgias and arthralgias. Three patients had grade 3 peripheral neuropathy. As expected, alopecia occurred in all patients, but four patients thus far have had regrowth of their hair while still being treated with paclitaxel at doses of 150 to 180 mg/m^2. As before, no significant cardiac or hypersensitivity toxicities were seen. One patient had dermatitis, which recalled a previous reaction to radiation.

DISCUSSION

Our experience confirms the impression of investigators from the M.D. Anderson Hospital[6]; that is, paclitaxel is a relatively well-tolerated and very active agent in the treatment of metastatic breast cancer. Of note is that the patients in our trials had many attributes that usually predict a poor response rate, including bone disease, the presence of many metastatic sites, and, in the second trial, truly extensive prior treatment. We are very encouraged that a patient achieved complete disappearance of tumor in a site that had previously been treated with radiation.

We also note with optimism a seeming lack of clinically apparent cross-resistance between doxorubicin and paclitaxel. Patients who received doxorubicin in the adjuvant setting and those whose macroscopic tumors demonstrated resistance to this drug were still able to benefit from paclitaxel. This is of special interest since cross-resistance to vinblastine has been observed experimentally,[13] suggesting a mechanism of resistance involving the multidrug resistance gene.[14] Cremophor EL has been reported to reverse multidrug resistance,[15] but the relevance of this observation to our results is unclear, especially considering the low level of systemic Cremophor EL likely achieved in our patients. Clearly, more laboratory and clinical work in this regard is needed.

Although we do not have randomized data for comparison, the use of rhG-CSF seems to ameliorate some of the neutropenia caused by paclitaxel. The cytokine certainly shortens the duration of marrow suppression. We intend to use this observation in the design of a dose-intensive regimen using paclitaxel more frequently than every 3 weeks. The 200 mg/m^2 dose seems tolerable in most patients, but it is unlikely that major escalations in dose will be possible unless newer hematologic support technologies (eg, peripheral blood stem cell infusions) are used, and dose-limiting neurotoxicity can be avoided. Yet, even if ongoing research establishes that there is no relationship between dose level of paclitaxel (once some threshold dose has been achieved) and response, there still may be advantages to increasing dose intensity, whatever the dose level, by shortening cycle length.[16]

So far, all of our data concern paclitaxel as a single agent. Combinations of paclitaxel with other agents are being studied in a wide variety of neoplastic diseases. The initial observation of the activity of paclitaxel in advanced ovarian cancer[10] led to the study of the sequential use of cisplatin and paclitaxel.[17] It was reported that the sequence of cisplatin followed by paclitaxel resulted in more significant myelotoxicity than the reverse sequence, possibly because the clearance of paclitaxel was adversely affected by the preceding cisplatin. Results from the ongoing phase I investigation of paclitaxel and cisplatin with rhG-CSF will be needed to define the appropriate dose levels of these agents in combination.[18]

Similarly, the toxicity of the sequence of doxorubicin and paclitaxel in the treatment of metastatic breast cancer may be dependent on schedule. Because of stomatitis and, despite the use of rhG-CSF, neutropenia with infection, the maximal tolerated doses have been reported as 125 mg/m^2 of paclitaxel and 48 mg/m^2 of doxorubicin, when given in that sequence.[19] The reverse schedule appears to be tolerated more easily: dose levels of 60 mg/m^2 doxorubicin followed by 180 mg/m^2 paclitaxel are presently under investigation.[20]

Despite relatively low dose levels achievable in the paclitaxel-doxorubicin sequence, 80% of patients who received this combination as first chemotherapy for stage IV disease obtained partial remissions. Response data for the doxorubicin-paclitaxel sequence are not yet available. Similarly, it is too early to estimate the toxicity or efficacy of paclitaxel in combination with cyclophosphamide, carboplatin, etoposide, topotecan, hexamethylmelamine, 5-fluorouracil and leucovorin, or edatrexate.

CONCLUSION

While paclitaxel combinations are being developed, and even if the drug can be given safely with other agents, single-agent administration may be useful clinically. The ability of paclitaxel to kill breast cancer cells resistant to cyclophosphamide and doxorubicin suggests that the drug may have a role in the treatment of high-risk stage II disease. Although the combination of doxorubicin and cyclophosphamide is effective adjuvant treatment, it does not cure all patients.[21] Based on mathematic models[16] and clinical data establishing the superiority of a sequential approach to strictly alternating chemotherapy,[22] we recently presented the feasibility of applying doxorubicin as a single agent fol-

lowed by high-dose cyclophosphamide plus rhG-CSF.[23] We are now planning to add dose-intense paclitaxel as a third component of such a regimen in an effort to eradicate cells resistant to both doxorubicin and cyclophosphamide.

Clearly, paclitaxel is a promising agent for the treatment of breast cancer. It is reasonable to expect that ongoing research will rapidly establish its important role in the management of this disease.

REFERENCES

1. Wall ME, Wani MC: Antineoplastic agents from plants. Ann Rev Pharmacol Toxicol 17:117-132, 1977
2. Schiff PB, Fant J, Horwitz SB: Promotion of microtubule assembly in vitro by Taxol. Nature 277:665-667, 1979
3. Manfredi JJ, Horwitz SB: Taxol: An antimitotic agent with a new mechanism of action. Pharmacol Ther 25:83-125, 1984
4. Rowinsky EK, Cazenave LA, Donehower RC: Taxol: A novel investigational antimicrotubule agent. J Natl Cancer Inst 82:1247-1259, 1990
5. Investigational Drug Branch, National Cancer Institute: Taxol (NSC 125973) [clinical brochure]. Bethesda, MD, National Cancer Institute, 1990
6. Holmes FA, Walters RS, Theriault RL, et al: Phase II trial of Taxol, an active drug in the treatment of metastatic breast cancer. J Natl Cancer Inst 83:1797-1805, 1991
7. Donehower RC, Rowinsky EK, Grochow LB, et al: Phase I trial of Taxol in patients with advanced cancer. Cancer Treat Rep 71:1171-1177, 1987
8. Wiernik PH, Schwartz EL, Einzig A: Phase I trial of Taxol given as a 24-hour infusion every 21 days: Responses observed in metastatic melanoma. J Clin Oncol 5:1232-1239, 1987
9. Lassus M, Scott D, Leyland-Jones B: Allergic reactions associated with cremaphor containing antineoplastics. Proc Am Soc Clin Oncol 4:268, 1985 (abstr)
10. McGuire WP, Rowinsky EK, Rosenshein NB, et al: Taxol: A unique antineoplastic agent with significant activity in ovarian epithelial neoplasms. Ann Intern Med 111:273-279, 1989
11. Legha SS, Ring S, Papadopoulos N: A phase II trial of Taxol in metastatic melanoma. Cancer 65:2478-2481, 1990
12. Kris MG, O'Connell JP, Gralla RJ: Phase I trial of Taxol given as a 3-hour infusion every 21 days. Cancer Treat Rep 70:605-607, 1986
13. Gupta RS: Cross-resistance of vinblastine and Taxol-resistant mutants of Chinese hamster ovary cells to other anticancer drugs. Cancer Treat Rep 69:515-521, 1985
14. Roy SN, Horwitz SB: A phosphoglycoprotein associated with Taxol resistance in J774.2 cells. Cancer Res 45:3856-3863, 1985
15. Woodcock DM, Jefferson S, Linsenmeyer ME, et al: Reversal of the multidrug resistance phenotype with Cremophor EL, a common vehicle for water-insoluble vitamins and drugs. Cancer Res 50:4199-4203, 1990
16. Norton L, Day R: Potential innovations in scheduling in cancer chemotherapy, in DeVita VT, Jr, Hellman S, Rosenberg SA (eds): Important Advances in Oncology 1991. Philadelphia, PA, Lippincott, 1991, pp 57-72
17. Rowinsky EK, Gilbert MR, McGuire WP, et al: Sequences of Taxol and cisplatin: A phase I and pharmacologic study. J Clin Oncol 9:1692-1703, 1991
18. Forastiere AA, Rowinsky E, Chaudry V, et al: Phase I trial of Taxol and cisplatin plus G-CSF in solid tumors. Proc Am Soc Clin Oncol 11:117, 1992 (abstr)
19. Holmes FA, Frye D, Valero V, et al: Phase I study of Taxol and doxorubicin with G-CSF in patients without prior chemotherapy for metastatic breast cancer. Proc Am Soc Clin Oncol 11:60, 1992 (abstr)
20. Holmes FA, Walters R, Valero V: The M.D. Anderson experience with Taxol in metastatic breast cancer. Proceedings of the 2nd National Cancer Institute Workshop on Taxol and *Taxus*, Alexandria, VA, September 1992
21. Fisher B, Brown AM, Dimitrov NV, et al: Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: Results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 8:1483-1496, 1990
22. Buzzoni R, Bonadonna G, Valagussa P, et al: Adjuvant chemotherapy with doxorubicin plus cyclophosphamide, methotrexate, and fluorouracil in the treatment of resectable breast cancer with more than three positive axillary nodes. J Clin Oncol 9:2134-2140, 1992
23. Hudis CA, Lebwohl D, Crown J, et al: Feasibility of adjuvant dose-intensive cyclophosphamide with G-CSF after doxorubicin in women with high risk stage II/III resectable breast cancer. Proc Am Soc Clin Oncol 11:55, 1992 (abstr)

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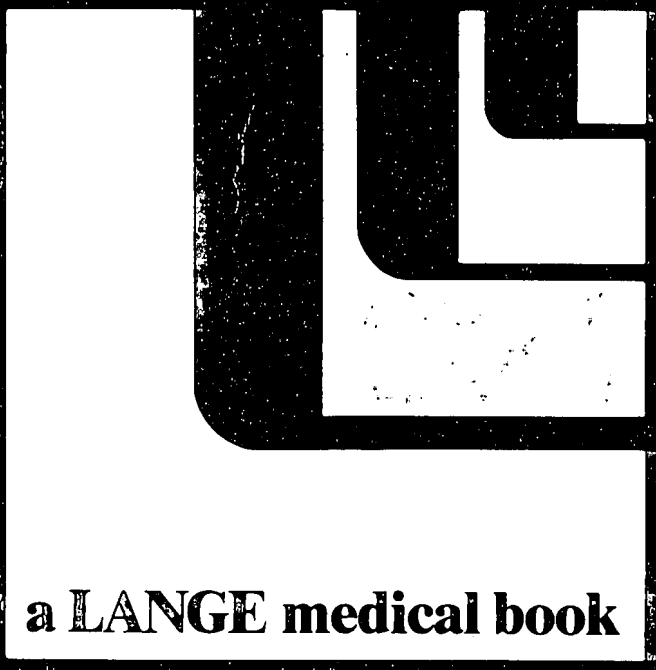

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Pharmacokinetics: Absorption, Distribution, & Elimination

3

Leslie Z. Benet, PhD

When a clinician prescribes a drug and the patient takes it, their main concern is with the effect on the patient's disease. However, as illustrated in Fig 3–1, several processes are going forward from the time a dose is administered until the appearance of any therapeutic effect. These pharmacokinetic processes, defined in Chapter 1, determine how rapidly and in what concentration and for how long the drug will appear at the target organ. The 3 steps shown in Fig 3–1—**bioavailability, distribution,** and **clearance**—are the major pharmacokinetic variables. In most cases, bioavailability will be defined as a measure of the speed and completeness of absorption from the most convenient site of administration. For most drugs, oral administration is appropriate, and measurable concentrations of the drug in the blood result. The pattern of the concentration-time curve in the blood is a function of the bioavailability, distribution, and clearance (or loss) factors. In this chapter, we will examine the quantitative aspects of these relationships.

A fundamental hypothesis of pharmacokinetics is that a pharmacodynamic relationship exists between a pharmacologic or toxic effect of a drug and the concentration of the drug in a readily accessible site of the body (eg, blood). This hypothesis has been documented for many drugs (Table 3–1), although for some drugs no clear relationship has been found between pharmacologic effect and plasma or blood concentrations. In most cases, the concentration of drug in the general circulation will be related to its concentration at the site of action. The drug will then elicit a number of pharmacologic effects at the site of action. These pharmacologic effects may include toxic effects in addition to the desired clinical response.

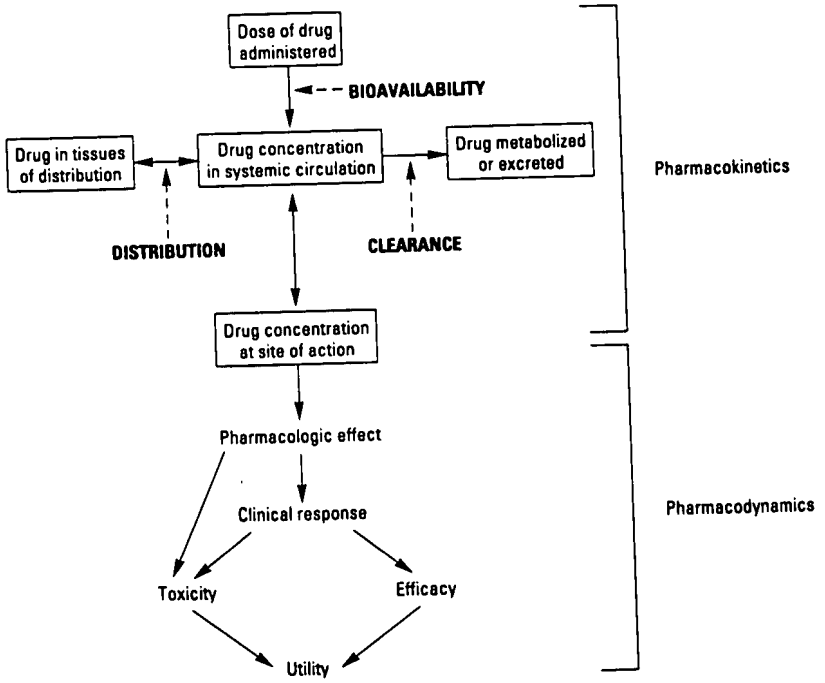

Figure 3–1. A schematic representation of the pharmacokinetic and pharmacodynamic processes that link administration of a drug to its effects.